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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/673,786	AKHVERDIAN ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/8/04, 12/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: alignment

DETAILED ACTION

Status of the Application

Claims 12-22 are pending.

Applicant's preliminary amendment of claim 12, cancellation of claims 1-11, and addition of claims 13-22 as submitted in a communication filed on 3/9/2006 is acknowledged.

Applicant's election with traverse of Group II, claim 12 drawn to a process for the preparation of L-threonine by culturing an L-threonine producing microorganism from the genus *Escherichia*, in a communication filed on 3/9/2006 is acknowledged.

Applicants traverse is on the grounds that there would be no burden on the Office to examine Groups I and II. This argument is not found persuasive. As previously indicated in the restriction requirement mailed on 2/9/2006, the inventions of Groups I-II belong to recognized divergent subject matter as evidenced by their different classification. Furthermore, a search of both inventions would require separate patented/non-patented literature searches as well as class/subclass searches, which are not all co-extensive. Different keywords would be required to search each of the inventions. Thus, a search of both inventions would impose an undue burden on the Office.

The requirement is deemed proper and therefore is made FINAL.

There are presently no claims directed to non-elected subject matter. Amended claim 12 and new claims 13-22 are directed to the elected subject matter. Thus, these claims are at issue and are being examined herein.

Priority

1. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to RUSSIAN FEDERATION 2002104983 filed on 02/27/2002. It is noted that the instant document is in English.

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 in the first paragraph of the specification to PCT/JP03/02067 filed on 02/25/2003. It is noted that this WIPO document is in Japanese and there is no record of a submission of a corresponding English translation. Applicants have indicated that the instant application is a continuation of PCT/JP03/02067. In view of the fact that the Examiner is unable to determine the contents of PCT/JP03/02067, and whether the contents of the foreign priority document have been included in PCT/JP03/02067, the Examiner will use the filing date of the instant application, 9/30/2003, for prior art purposes.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 1/8/2004 and 12/22/2004 are acknowledged. The references cited in the International Search Report of PCT/JP03/02067 have been cited in the IDS of 1/8/2004. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

4. Claim 19 is objected to due to the recitation of "DNA which is hybridizable with a nucleotide sequence of the nucleotides ...". As known in the art, hybridization takes place between nucleic acid molecules. Nucleotide sequences are graphical representations of the order in which nucleotides are arranged in a nucleic acid molecule. Therefore, it is suggested that the claim be amended to make it clear that the DNA recited in the claim hybridizes to another nucleic acid molecule and not to a graphical representation of such molecule. Appropriate correction is required.

5. Claim 21 is objected to due to the recitation of "d) the rhtA gene, which codes for putative transmembrane protein, and e) and combinations thereof" in view of the fact that the term "and" has been recited twice. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 14-16, 19 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 14 (claims 15-16 dependent thereon) is indefinite in the recitation of "copy number of the aspartate aminotransferase gene" as there is no antecedent basis for "the aspartate aminotransferase gene" in claim 12, from which claim 14 depends. Correction is required.

9. Claim 19 is indefinite in the recitation of the term "DNA which is hybridizable.....under stringent conditions" for the following reasons. It is unclear which polynucleotide is being recited absent a statement of the conditions under which the hybridization reaction is performed. Nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions. While the specification exemplifies conditions which Applicants considered stringent, there is no definition in the specification as to what is encompassed by the term. For examination purposes, it will be assumed that the term "stringent conditions" reads "any conditions". Correction is required.

10. Claim 21 is indefinite in the recitation of "the mutant thrA gene", "the thrC gene", "the rhtA gene" as there is no antecedent basis for these genes in claim 13, from which claim 21 depends. For examination purposes, the term "the" will be interpreted as "a". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 12-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12-20 are directed to a method for the production of L-threonine wherein said method comprises cultivating an L-threonine-producing *Escherichia* bacterium which comprises a polynucleotide encoding a genus of aspartate aminotransferases, a polynucleotide encoding a genus of *Escherichia* aspartate aminotransferases, or a polynucleotide which hybridize under any conditions to any fragment within the nucleic acid of SEQ ID NO: 1 and encode a genus of aspartate aminotransferases, wherein (1) said *Escherichia* bacterium has been modified in any way to enhance the activity of said aspartate aminotransferases, (2) said aspartate aminotransferases have been modified in any way to enhance their enzymatic activity, (3) the expression of said polynucleotides is increased by using any method, and/or (4) the expression control elements of any gene encoding said aspartate aminotransferases have been modified in any way. Claims 21-22 are directed to the method of claim 13 wherein said bacterium has also been modified in any way to enhance expression of a nucleic acid encoding a genus of mutant aspartokinase homoserine dehydrogenases I, homoserine kinases, threonine synthases, and/or transmembrane proteins. It is noted that a protein comprising SEQ ID NO: 2 with any number of deletions, substitutions or insertions, wherein said protein has aspartate aminotransferase activity is no different from a protein having any structure and having aspartate aminotransferase activity since there is no limit as to how many modifications can be made to the protein of SEQ ID NO: 2. Furthermore, the term "a nucleotide sequence of the nucleotides 1 to 1191 in SEQ ID NO: 1" has been broadly interpreted by the Examiner in accordance with MPEP 2111.01 to encompass a fragment of any size of the polynucleotide of SEQ ID NO: 1 (1191 nucleotides) since the term can be interpreted as "nucleotide

sequence within nucleotides 1 to 1191 of SEQ ID NO: 1". See Claim Rejections under 35 USC 112, second paragraph for claim interpretation as it relates to the term "stringent conditions".

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The claims require an extremely large genus of nucleic acids encoding aspartate aminotransferases. In addition, the claims require (1) unknown mutations in any aspartate aminotransferase to enhance their enzymatic activity, (2) unknown modifications in the expression control elements of any gene encoding an aspartate aminotransferase to enhance their expression, such as mutations in the promoter region, (3) unknown methods to enhance the activity of any aspartate aminotransferase, such as the addition of chemical compounds or biological compounds which when in contact with any aspartate aminotransferase would increase their enzymatic activity (e.g., agonists), and (4) unknown methods to increase expression of any nucleic acid encoding an aspartate aminotransferase,

aspartokinase homoserine dehydrogenase I, homoserine kinase, threonine synthase, or transmembrane protein, such as transcriptional activators.

While the specification and/or the art disclose (1) a few aspartate aminotransferases (and their corresponding coding nucleic acids) in a few organisms, such as the *E. coli* aspartate aminotransferase, and (2) increased activity of an enzyme by overexpression of a nucleic acid encoding the enzyme wherein said overexpression is the result of increasing the copy number of said nucleic acid, or using strong heterologous promoters well known in the art, the specification fails to disclose the structure of all the nucleic acids encoding aspartate aminotransferases as recited in the claims, other methods to enhance the enzymatic activity of any aspartate aminotransferase, other methods to increase expression of any nucleic acid encoding an aspartate aminotransferase, aspartokinase homoserine dehydrogenase I, homoserine kinase, threonine synthase, or transmembrane protein, modifications in the expression control elements of any gene encoding an aspartate aminotransferase, or mutations in any aspartate aminotransferase which would result in increased enzymatic activity.

The claims require a genus of nucleic acids which are structurally unrelated. A sufficient written description of a genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides defined by their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is either (1) no structural feature which is representative of all the members of the genus of nucleic acids required in the claimed invention, or (2) the recited structural feature recited (i.e., DNA which is hybridizable.....under any conditions to any fragment of the nucleic acid of SEQ ID NO: 1) does not constitute a substantial portion of the genus as the remainder of the structure of any nucleic acid encoding a polypeptide having aspartate aminotransferase activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. There is no information as to a correlation between the structures disclosed/known in the art and

aspartate aminotransferase activity. Furthermore, while one could argue that the structures of known nucleic acids encoding aspartate aminotransferases are representative of all members of the genus of nucleic acids required, such that the claimed invention is adequately described, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with aspartate aminotransferase activity has been provided, one cannot reasonably conclude that the known structures are representative of all the nucleic acids required in the claimed invention.

Due to the fact that the specification only discloses (1) the polynucleotide of SEQ ID NO: 1, and (2) a single method to increase enzymatic activity, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

13. Claims 12-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of L-threonine wherein said method comprises cultivating an L-threonine-producing *Escherichia* bacterium which overexpresses a polynucleotide encoding the polypeptide of SEQ ID NO: 2, and wherein said overexpression results from increasing the copy number of said polynucleotide, does not reasonably provide enablement for a method for the production of L-threonine wherein said method comprises cultivating an L-threonine-producing *Escherichia* bacterium which comprises a polynucleotide encoding any aspartate aminotransferase or any *Escherichia* aspartate aminotransferase, or a polynucleotide which hybridizes under any conditions to any fragment of the

polynucleotide of SEQ ID NO: 1 and encode any aspartate aminotransferase, wherein (1) said *Escherichia* bacterium has been modified in any way to enhance the activity of said aspartate aminotransferases, (2) said aspartate aminotransferases have been modified in any way to enhance their enzymatic activity, (3) the expression of said polynucleotides and the expression of polynucleotides encoding mutant aspartokinase homoserine dehydrogenases I, homoserine kinases, threonine synthases, and/or transmembrane proteins are increased by using any method, or (4) the expression control elements of any gene encoding said aspartate aminotransferases have been modified in any way. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 12-22 are so broad as to encompass a method for the production of L-threonine wherein said method comprises cultivating an L-threonine-producing *Escherichia* bacterium which comprises a polynucleotide encoding any aspartate aminotransferase, a polynucleotide encoding any *Escherichia* aspartate aminotransferase, or a polynucleotide which hybridizes under any conditions to any fragment within the nucleic acid of SEQ ID NO: 1 and encode any aspartate aminotransferase, wherein (1) said *Escherichia* bacterium has been modified in any way to enhance the activity of said aspartate aminotransferases, (2) said aspartate aminotransferases have been modified in any way to enhance their enzymatic activity, (3) the expression of said polynucleotides and

the expression of polynucleotides encoding mutant aspartokinase homoserine dehydrogenases I, homoserine kinases, threonine synthases, and/or transmembrane proteins are increased by using any method, and/or (4) the expression control elements of any gene encoding said aspartate aminotransferase have been modified in any way. See Claim Rejections under 35 USC 112, second paragraph and written description rejection above for discussion regarding claim interpretation. The enablement provided is not commensurate in scope with the claims due to the extremely large number of nucleic acids encoding aspartate aminotransferases for which there is no structure disclosed, as well as the unknown methods which would allow (1) increased aspartate aminotransferase activity, and (2) increased expression of nucleic acids encoding aspartate aminotransferases or other proteins. In the instant case, the specification enables a method for the production of L-threonine wherein said method comprises cultivating an L-threonine-producing *Escherichia* bacterium which overexpresses a polynucleotide encoding the polypeptide of SEQ ID NO: 2, and wherein said overexpression results from increasing the copy number of said polynucleotide.

The amount of direction or guidance presented and the existence of working examples. The specification discloses an L-threonine *E. coli* strain which overexpresses a nucleic acid encoding the polypeptide of SEQ ID NO:2 and produces L-threonine, as a working example. However, the specification fails to disclose (1) other methods to obtain enhanced aspartate aminotransferase activity, or (2) other methods to increase expression of a nucleic acid encoding an aspartate aminotransferase, mutant aspartokinase homoserine dehydrogenase I, homoserine kinase, threonine synthase, and/or transmembrane protein, or (3) the structure of nucleic acids encoding aspartate aminotransferases.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The nucleotide sequence of a nucleic acid encoding a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and aspartate aminotransferase activity such that one of skill in

the art can envision the structure of any nucleic acid encoding an aspartate aminotransferase. In addition, neither the art nor the specification provide any teaching or guidance as to which structural elements in those aspartate aminotransferases known in the art, or in the polypeptide of SEQ ID NO: 2, should be present in any aspartate aminotransferase. The art clearly teaches the high level of unpredictability with regard to the effect of structural changes in a protein's activity when no guidance/knowledge as to which amino acids are required for activity has been provided. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polynucleotide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for (1) all nucleic acids encoding aspartate aminotransferases, (2) an essentially infinite number of mutations within expression control elements of any gene encoding an aspartate aminotransferase to obtain higher expression, (3) any chemical/biological compound which would increase aspartate aminotransferase activity or increase expression of any nucleic acid encoding an aspartate aminotransferase, mutant aspartokinase homoserine dehydrogenase I, homoserine kinase,

threonine synthase, and/or transmembrane protein, or (4) any mutation in any aspartate aminotransferase which would result in increased enzymatic activity. In the absence of (1) a correlation between structure and aspartate aminotransferase activity, (2) some guidance as to which are the structural changes within the expression control elements of any gene encoding an aspartate aminotransferase would result in increased expression, (3) some guidance as to the structural changes required in any aspartate aminotransferase to increase enzymatic activity, or (4) some guidance as to what is required in any compound which increases aspartate aminotransferase activity or increases expression of nucleic acids encoding aspartate aminotransferases, mutant aspartokinase homoserine dehydrogenases I, homoserine kinases, threonine synthases, and/or transmembrane proteins, one of skill in the art would have to (1) test an essentially infinite number of polynucleotides to determine (i) which ones encode aspartate aminotransferases, or (ii) which ones encode aspartate aminotransferases with enhanced enzymatic activity, (2) test an essentially infinite number of modifications, including modifications within the expression control elements of a gene encoding an aspartate aminotransferase, to determine which ones would result in increased expression of a nucleic acid encoding an aspartate aminotransferase, a mutant aspartokinase homoserine dehydrogenase I, a homoserine kinase, a threonine synthase, and/or a transmembrane protein, and/or (3) test an essentially infinite number of compounds/biologicals to determine which ones enhance aspartate aminotransferase activity or expression of nucleic acids encoding aspartate aminotransferases, mutant aspartokinase homoserine dehydrogenases I, homoserine kinases, threonine synthases, and/or transmembrane proteins.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided

sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 12-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katsumata et al. (EP 0219027 published 4/22/1987; cited in the IDS) in view of Debabov et al. (U.S. Patent No. 5175107 issued on 12/29/1992; cited in the IDS), Edwards et al. (WO 87/00202 published on 1/15/1987; cited in the IDS), and further in view of Kishino et al. (U.S. Patent No. 6319696 issued on 11/20/2001).

Katsumata et al. teach a process for the production of L-threonine by a *C. glutamicum* cell wherein said *C. glutamicum* cell is transformed with a plasmid comprising a *C. glutamicum* gene encoding aspartate aminotransferase (page 17, line 26-page 19, line 31; page 20, line 25-page 21, line 20). Katsumata et al. does not teach production of L-threonine by an *Escherichia* bacterium or the aspartate aminotransferase of SEQ ID NO: 2. Debabov et al. teach an *E. coli* cell which is a high threonine

producer (VKPM B-3996) and has been modified to enhance the expression of a mutant aspartokinase homoserine dehydrogenase 1 resistant to feedback inhibition by threonine (thrA), a gene encoding a homoserine kinase (thrB), a gene encoding a threonine synthase (thrC), and a gene encoding a transmembrane protein (rhtA) (Figure 1; column 1, lines 20-41; column 2, line 68-column 3, line 14). Debabov et al. does not teach the aspartate aminotransferase of SEQ ID NO: 2. Edwards et al. teach the production of several amino acids (page 18, line 21-34) by culturing an *E. coli* cell which overexpresses a gene comprising SEQ ID NO: 1 (encodes the polypeptide of SEQ ID NO: 2). See attached alignment provided for visualization purposes (SEQ ID NO: 12 in the sequence listing of that reference is the same as SEQ ID NO: 2 of the instant reference). Edwards et al. does not teach production of L-threonine or an *E. coli* cell which is further modified to increase the expression of a mutant gene encoding an aspartokinase homoserine dehydrogenase 1 resistant to feedback inhibition by threonine, a gene encoding a homoserine kinase, a gene encoding a threonine synthase, and/or a gene encoding a transmembrane protein. Kishino et al. teach production of L-threonine by culturing *E. coli* cells transformed with vectors that express *E. coli* genes encoding enzymes directly associated with the biosynthesis of L-threonine. Kishino et al. teach the use of low copy vectors (such as pBR322; column 5, lines 36-40) and also teach that the *E. coli* strain VKPM B-3996 (described above) is a preferred strain for the production of L-threonine due to its high threonine yields (column 4, lines 7-9). Kishino et al. does not teach production of L-threonine by culturing an *E. coli* cell transformed with a vector comprising the nucleic acid of SEQ ID NO: 1.

Claims 12-15 and 18 (partially) are directed in part to a method for producing L-threonine which requires an *Escherichia* bacterium modified to enhance the activity of an aspartate aminotransferase by increasing the copy number of a gene encoding the aspartate aminotransferase. Claim 16 is directed to the method of claim 15 with the added limitation that the copy number is increased via a low-copy number vector. Claims 17 and 18-20 (partially) are directed in part to the method of claim 13 wherein the

aspartate aminotransferase comprises SEQ ID NO: 2, the gene encoding the aspartate aminotransferase comprises SEQ ID NO: 1, or the gene encoding the aspartate aminotransferase hybridizes under specific conditions to any fragment of the polynucleotide of SEQ ID NO: 1. Claims 21-22 are directed in part to the method of claim 13 wherein the *Escherichia* bacterium is further modified to increase the expression of a mutant gene encoding an aspartokinase homoserine dehydrogenase 1 resistant to feedback inhibition by threonine, a gene encoding a homoserine kinase, a gene encoding a threonine synthase, and a gene encoding a transmembrane protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to transform the *E. coli* strain of Debabov et al. with the low copy number vector of Kishino et al., wherein said vector comprises the nucleic acid of Edwards et al. for the production of L-threonine. A person of ordinary skill in the art is motivated to create the *E. coli* cell of Debabov, Kishino and Edwards and culture said cell to produce L-threonine in view of the fact that (1) Katsumata et al. teach the production of L-threonine by culturing a microorganism transformed with a vector comprising the endogenous gene encoding aspartate aminotransferase so that the level of aspartate aminotransferase is increased in the microorganism, (2) Kishino et al. teach that high threonine producers, such as the strain of Debabov et al., are preferred strains for L-threonine production, (3) the polypeptide of SEQ ID NO: 2 is the *E. coli* aspartate aminotransferase and is preferred as it is the endogenous enzyme for the *E. coli* strain of Debabov et al. and would not be recognized by the cell as foreign, (4) a low copy number vector would be preferable to better control how much of the aspartate aminotransferase is produced and avoid intracellular instability, and (5) aspartate aminotransferase catalyzes the conversion of oxaloacetate to aspartate, which is a precursor of L-threonine.

One of ordinary skill in the art has a reasonable expectation of success at inserting the DNA of Edwards et al. in a low copy vector such as that of Kishino et al., transform the *E. coli* strain of Debabov et al., and culture the resulting recombinant microorganism for the production of L-threonine since (1)

cloning of genes in low copy vectors and transformation of *E. coli* cells with low copy vectors is well known and widely used in the art, (2) increasing the levels of aspartate aminotransferase should result in an increase in aspartate, which in turn should result in increasing levels of L-threonine, and (3) Katsumata et al. teach L-threonine production by culturing a microorganism wherein the endogenous aspartate aminotransferase levels are increased. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

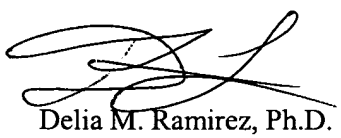
17. No claim is in condition for allowance.

18. The cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
May 12, 2006

PD 22-JUL-1998.
XX
PF 05-DEC-1997; 97EP-00121443.
XX
PR 05-DEC-1996; 96JP-00325659.
XX
PA (AJIN) AJINOMOTO CO INC.
XX
PI Araki M, Sugimoto M, Yoshihara Y, Nakamatsu T;
XX
DR WPI; 1998-379060/33.
DR P-PSDB; AAW69553.
XX
PT Recombinant DNA autonomously replicable in coryneform bacteria - used to
PT produce L-lysine, codes for e.g. aspartokinase, di:hydropicolinate
PT reductase and synthase and di:amino-pimelate decarboxylase.
XX
PS Example 5; Page 37-38; 59pp; English.
XX
CC The present invention describes a recombinant DNA autonomously replicable
CC in cells of coryneform bacteria (CB), comprising a DNA sequence coding
CC for an aspartokinase (AK) in which feedback inhibition by L-lysine and L-
CC threonine is desensitised, a DNA sequence coding for a
CC dihydrodipicolinate reductase (DHPR), a DNA sequence coding for
CC dihydropicolinate synthase (DHPS), a DNA sequence coding for
CC diaminopimelate decarboxylase (DAMD) and a DNA sequence coding for
CC aspartate aminotransferase (AAT). The present sequence encodes aspC from
CC Escherichia coli. The DNA and related products from the present
CC invention, can be used for improving L-lysine productivity by CB. The L-
CC lysine produced can be used as a fodder additive
XX
SQ Sequence 1331 BP; 330 A; 340 C; 350 G; 311 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	1.03e-202	Length:	1331
Score:	2045.00	Matches:	396
Percent Similarity:	100.0%	Conservative:	0
Best Local Similarity:	100.0%	Mismatches:	0
Query Match:	100.0%	Indels:	0
DB:	2	Gaps:	0

US-10-673-786A-2 (1-396) x AAV40259 (1-1331)

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Db         10 ATGTTTGAGAACATTACCGCCGCTCCTGCCGACCCGATTCTGGGCCTGGCCGATCTGTTT 69

Qy         21 ArgAlaAspGluArgProGlyLysIleAsnLeuGlyIleGlyValTyrLysAspGluThr 40
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Db         70 CGTGCCGATGAACGTCCCGGCAAAATTAACCTCGGGATTGGTGTCTATAAAGATGAGACG 129

Qy         41 GlyLysThrProValLeuThrSerValLysLysAlaGluGlnTyrLeuLeuGluAsnGlu 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        130 GGCAAAACCCCGGTACTGACCAGCGTGAAAAAGGCTGAACAGTATCTGCTCGAAAATGAA 189

Qy         61 ThrThrLysAsnTyrLeuGlyIleAspGlyIleProGluPheGlyArgCysThrGlnGlu 80
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Qy         81 LeuLeuPheGlyLysGlySerAlaLeuIleAsnAspLysArgAlaArgThrAlaGlnThr 100
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Qy        101 ProGlyGlyThrGlyAlaLeuArgValAlaAlaAspPheLeuAlaLysAsnThrSerVal 120
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Db        310 CCGGGGGGCACTGGCGCACTACGCGTGGCTGCCGATTTCCTGGCAAAAAATACCAGCGTT 369

Qy        121 LysArgValTrpValSerAsnProSerTrpProAsnHisLysSerValPheAsnSerAla 140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy        141 GlyLeuGluValArgGluTyrAlaTyrTyrAspAlaGluAsnHisThrLeuAspPheAsp 160
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Db        430 GGTCTGGAAGTTCGTGAATACGCTTATTATGATGCGGAAAATCACACTCTTGACTTCGAT 489

Qy        161 AlaLeuIleAsnSerLeuAsnGluAlaGlnAlaGlyAspValValLeuPheHisGlyCys 180
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Db        490 GCACTGATTAACAGCCTGAATGAAGCTCAGGCTGGCGACGTAGTGCTGTTCCATGGCTGC 549

Qy        181 CysHisAsnProThrGlyIleAspProThrLeuGluGlnTrpGlnThrLeuAlaGlnLeu 200
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Qy        201 SerValGluLysGlyTrpLeuProLeuPheAspPheAlaTyrGlnGlyPheAlaArgGly 220
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Db        610 TCCGTTGAGAAAGGCTGGTTACCGCTGTTTGACTTCGCTTACCAGGGTTTTGCCCGTGGT 669

Qy        221 LeuGluGluAspAlaGluGlyLeuArgAlaPheAlaAlaMetHisLysGluLeuIleVal 240
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Db        670 CTGGAAGAAGATGCTGAAGGACTGCGCGCTTTCGCGGCTATGCATAAAGAGCTGATTGTT 729

Qy        241 AlaSerSerTyrSerLysAsnPheGlyLeuTyrAsnGluArgValGlyAlaCysThrLeu 260
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Db        730 GCCAGTTCCTACTCTAAAAACTTTGGCCTGTACAACGAGCGTGTTGGCGCTTGTACTCTG 789

Qy        261 ValAlaAlaAspSerGluThrValAspArgAlaPheSerGlnMetLysAlaAlaIleArg 280
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        790 GTTGCTGCCGACAGTGAAACCGTTGATCGCGCATTCAGCCAAATGAAAGCGGCGATTCGC 849

Qy        281 AlaAsnTyrSerAsnProProAlaHisGlyAlaSerValValAlaThrIleLeuSerAsn 300
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Qy        301 AspAlaLeuArgAlaIleTrpGluGlnGluLeuThrAspMetArgGlnArgIleGlnArg 320
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Db        910 GATGCGTTACGTGCGATTTGGGAACAAGAGCTGACTGATATGCGCCAGCGTATTCAGCGT 969

Qy        321 MetArgGlnLeuPheValAsnThrLeuGlnGluLysGlyAlaAsnArgAspPheSerPhe 340
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        970 ATGCGTCAGTTGTTCGTCAATACGCTGCAGGAAAAAGGCGCAAACCGCGACTTCAGCTTT 1029

Qy        341 IleIleLysGlnAsnGlyMetPheSerPheSerGlyLeuThrLysGluGlnValLeuArg 360
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Db       1030 ATCATCAAACAGAACGGCATGTTCTCCTTCAGTGGCCTGACAAAAGAACAAGTGCTGCGT 1089

Qy        361 LeuArgGluGluPheGlyValTyrAlaValAlaSerGlyArgValAsnValAlaGlyMet 380
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Db       1090 CTGCGCGAAGAGTTTGGCGTATATGCGGTTGCTTCTGGTCGCGTAAATGTGGCCGGGATG 1149

Qy        381 ThrProAspAsnMetAlaProLeuCysGluAlaIleValAlaValLeu 396
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Db       1150 ACACCAGATAACATGGCTCCGCTGTGCGAAGCGATTGTGGCAGTGCTG 1197
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RESULT 5
AAN71109
ID AAN71109 standard; DNA; 3659 BP.
XX
AC AAN71109;
XX
DT 01-JAN-1980 (first entry)
XX
DE pheA aroF aspC operon in plasmid pME219.
XX
KW alpha-amylase; feedback inhibition; amino acid synthesis;
KW composite plasmid; ss.
XX
OS Bacillus licheniformis.
XX

FH	Key	Location/Qualifiers
FT	CDS	69. .1241
FT		/*tag= a
FT	CDS	1259. .2329
FT		/*tag= b
FT	CDS	2344. .3534
FT		/*tag= c

XX

PN WO8700202-A.
XX
PD 15-JAN-1987.
XX
PF 24-JUN-1986; 86WO-US001353.
XX
PR 24-JUN-1985; 85US-00747732.
XX
PA (NUTR-) NUTRASWEET CO.
XX
PI Edwards MR, Taylor PP, Hunter MG, Fotheringh IG;
XX
DR WPI; 1987-021998/03.
DR P-PSDB; AAP70752, AAP71677, AAP71678.
XX
PT Composite plasmids contg. multiple genes in transcriptional units -
PT useful for prodn. of aminoacid(s), esp. L-phenylalanine and l-tyrosine.
XX
PS Disclosure; Page 38; 57pp; English.
XX
CC This sequence may be inserted into a composite plasmid and used for the
CC production of amino acids. See also AAN71053-55, AAN71107, AAN71109,
CC AAN71111 and AAP70696-97 and AAP70750, AAP70752 and AAP70754
XX
SQ Sequence 3659 BP; 936 A; 911 C; 947 G; 865 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	4.19e-202	Length:	3659
Score:	2045.00	Matches:	396
Percent Similarity:	100.0%	Conservative:	0
Best Local Similarity:	100.0%	Mismatches:	0
Query Match:	100.0%	Indels:	0
DB:	1	Gaps:	0

US-10-673-786A-2 (1-396) x AAN71109 (1-3659)

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Db       2344 ATGTTTGAGAACATTACCGCCGCTCCTGCCGACCCGATTCTGGGCCTGGCCGATCTGTTT 2403

Qy         21 ArgAlaAspGluArgProGlyLysIleAsnLeuGlyIleGlyValTyrLysAspGluThr 40
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Db       2404 CGTGCCGATGAACGTCCCGGCAAAATTAACCTCGGGATTGGTGTCTATAAAGATGAGACG 2463

Qy         41 GlyLysThrProValLeuThrSerValLysLysAlaGluGlnTyrLeuLeuGluAsnGlu 60
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Db       2464 GGCAAAACCCCGGTACTGACCAGCGTGAAAAAGGCTGAACAGTATCTGCTCGAAAATGAA 2523

Qy         61 ThrThrLysAsnTyrLeuGlyIleAspGlyIleProGluPheGlyArgCysThrGlnGlu 80
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Qy         81 LeuLeuPheGlyLysGlySerAlaLeuIleAsnAspLysArgAlaArgThrAlaGlnThr 100
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Qy        101 ProGlyGlyThrGlyAlaLeuArgValAlaAlaAspPheLeuAlaLysAsnThrSerVal 120
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Db       2644 CCGGGGGGCACTGGCGCACTACGCGTGGCTGCCGATTTCCTGGCAAAAAATACCAGCGTT 2703

Qy        121 LysArgValTrpValSerAsnProSerTrpProAsnHisLysSerValPheAsnSerAla 140
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Db       2704 AAGCGTGTGTGGGTGAGCAACCCAAGCTGGCCGAACCATAAGAGCGTCTTTAACTCTGCA 2763

Qy        141 GlyLeuGluValArgGluTyrAlaTyrTyrAspAlaGluAsnHisThrLeuAspPheAsp 160
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Db       2764 GGTCTGGAAGTTCGTGAATACGCTTATTATGATGCGGAAAATCACACTCTTGACTTCGAT 2823

Qy        161 AlaLeuIleAsnSerLeuAsnGluAlaGlnAlaGlyAspValValLeuPheHisGlyCys 180
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Db       2824 GCACTGATTAACAGCCTGAATGAAGCTCAGGCTGGCGACGTAGTGCTGTTCCATGGCTGC 2883

Qy        181 CysHisAsnProThrGlyIleAspProThrLeuGluGlnTrpGlnThrLeuAlaGlnLeu 200
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Db       2884 TGCCATAACCCAACCGGTATCGACCCTACGCTGGAACAATGGCAAACACTGGCACAACTC 2943

Qy        201 SerValGluLysGlyTrpLeuProLeuPheAspPheAlaTyrGlnGlyPheAlaArgGly 220
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Db       2944 TCCGTTGAGAAAGGCTGGTTACCGCTGTTTGACTTCGCTTACCAGGGTTTTGCCCGTGGT 3003

Qy        221 LeuGluGluAspAlaGluGlyLeuArgAlaPheAlaAlaMetHisLysGluLeuIleVal 240
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Db       3004 CTGGAAGAAGATGCTGAAGGACTGCGCGCTTTCGCGGCTATGCATAAAGAGCTGATTGTT 3063

Qy        241 AlaSerSerTyrSerLysAsnPheGlyLeuTyrAsnGluArgValGlyAlaCysThrLeu 260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3064 GCCAGTTCCTACTCTAAAAACTTTGGCCTGTACAACGAGCGTGTTGGCGCTTGTACTCTG 3123

Qy        261 ValAlaAlaAspSerGluThrValAspArgAlaPheSerGlnMetLysAlaAlaIleArg 280
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3124 GTTGCTGCCGACAGTGAAACCGTTGATCGCGCATTCAGCCAAATGAAAGCGGCGATTCGC 3183

Qy        281 AlaAsnTyrSerAsnProProAlaHisGlyAlaSerValValAlaThrIleLeuSerAsn 300
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Qy        301 AspAlaLeuArgAlaIleTrpGluGlnGluLeuThrAspMetArgGlnArgIleGlnArg 320
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Db       3244 GATGCGTTACGTGCGATTTGGGAACAAGAGCTGACTGATATGCGCCAGCGTATTCAGCGT 3303

Qy        321 MetArgGlnLeuPheValAsnThrLeuGlnGluLysGlyAlaAsnArgAspPheSerPhe 340
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Qy        341 IleIleLysGlnAsnGlyMetPheSerPheSerGlyLeuThrLysGluGlnValLeuArg 360
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Db       3424 CTGCGCGAAGAGTTTGGCGTATATGCGGTTGCTTCTGGTCGCGTAAATGTGGCCGGGATG 3483

Qy        381 ThrProAspAsnMetAlaProLeuCysGluAlaIleValAlaValLeu 396
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Db       3484 ACACCAGATAACATGGCTCCGCTGTGCGAAGCGATTGTGGCAGTGCTG 3531
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RESULT 6
AAS46273/c
ID AAS46273 standard; DNA; 14759 BP.
XX
AC AAS46273;
XX
DT 18-DEC-2001 (first entry)
XX
DE DNA encoding novel mar regulated protein (NIMR) #42.
XX
KW mar regulated polypeptide; NIMR; microbial infection; antibacterial; ds.
XX
OS Escherichia coli.
XX
PN WO200170776-A2.
XX
PD 27-SEP-2001.
XX
PF 08-MAR-2001; 2001WO-US007478.
XX
PR 10-MAR-2000; 2000US-0188362P.
XX
PA (TUFT) TUFTS COLLEGE.
XX
PI Levy SB, Barbosa TM, Alekshun MN;
XX
DR WPI; 2001-602769/68.
DR P-PSDB; AAU29374.
XX
PT Identifying compounds that modulate a newly identified mar regulated